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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/782,339	02/19/2004	Michael A. Siani-Rose	3582.1	5409

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EXAMINER	
WONG, JENNIFER SHIN SHIN	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 11/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/782,339	SIANI-ROSE, MICHAEL A.	
	Examiner	Art Unit	
	Jennifer Wong	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/14/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Claim Objections

1. The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not).

There are two claim number 5. The latter misnumbered claim 5 has been renumbered 6.

2. The use of the trademark HuSNP Mapping Assay has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology. The specification should be amended to capitalize the trademark wherever it appears and to include the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3-6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 3 are 4 are indefinite because do not recite a clear nexus between the preamble of the claims and the final process step of the claims. The claims are drawn to methods for correlating a polymorphism with a susceptibility to a disease. However, the claims recite a final step of detecting a disease-specific polymorphism. The claims do not clearly set forth the relationship between detecting a disease-specific polymorphism and correlating a polymorphism with a susceptibility to a disease. Thereby, it is unclear as to whether the claims are intended to be limited to methods correlating a polymorphism with a susceptibility to a disease or methods for detecting a disease-specific polymorphism.

Claims 5 and 6 are indefinite because do not recite a clear nexus between the preamble of the claims and the process of the claims. The claims are drawn to methods for predicting an immune response. However, the claims recite a final step of determining the clinical outcome of a patient. The claims do not clearly set forth the relationship between determining the clinical outcome of a patient and predicting an immune response. Thereby, it is unclear as to whether the claims are intended to be limited to methods for determining the clinical outcome of a patient or methods of predicting an immune response. In the later case, the claims are further unclear as to how the step of genotyping a patient's T cell receptor results in the prediction of a patient's immune response to a disease.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to

> be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-6 rejected under 35 U.S.C. 103(a) as being as being unpatentable over Maksymowych et al. (1992) in view of Shimkets et al. (WO 01/48245A2).

Maksymowych teaches a method to detect a T-cell receptor β chain (Tcrb), a component of the variable region of the T-cell receptor, gene allelic variant Tcrb-V6.1, and the presence of the said variant allele is indicative of juvenile rheumatoid arthritis, wherein the method comprises: 1) obtaining samples from juvenile rheumatoid arthritis patients and a control group; 2) radioactively labeling a probe specific for the variant region of the allele; 3) isolating and amplifying the DNA from the patient and control groups; and 4) performing a dot blot analysis.

With respect to the invention's method step 1, it requires the obtaining samples from patients and a control group. Maksymowych teaches "one hundred and twenty-six unrelated Caucasian patients, well characterized with respect to HLA markers, were studied. All had early-onset pauciarticular juvenile rheumatoid arthritis (EOPA-JRA) as defined by the American College of Rheumatology criteria....The control group ...resembled the disease population" (page 258). The specification teaches that the invention's method includes "obtaining a first nucleic acid from a population of individuals with a selected disease and a second nucleic acid from a control population of healthy individuals" (page 3, lines 2-4). The specification further defines that the said

disease is an autoimmune disease (page 15, lines 12-14). With respect to the invention's method step 2, Maksymowych shows that a cDNA probe derived from a cell line with "the V6.1, D, J, and C2 regions of the Tcrb chain ...was subcloned in pUC19, and a specific V region probe was derived by polymerase chain reaction amplification of the V region sequence using specific primers. The probe was labeled by...[α-^{32} P]-deoxynucleotide triphosphates" (page 258). Maksymowych teaches that the "members of the patient and control populations...were oligotyped for Tcrb-V6.1 gene allelic sequence variants" by a dot-blot analysis assay (page 258). The samples are hybridized to a membrane filter, probed with the labeled probes, and subsequently exposed to Kodak X-omat film (page 258). Experimental results comparing "HLA type revealed that HLA-DQA1*0101 patients differed significantly in their genotype distribution from HLA-DQA1*0101 controls.... HLA-DQA1*0101 patients had a higher frequency of the 12.5 kb *Bgl* II fragment than did either HLA-DQA1*0101 controls...or HLA-DQA1*0101 negative patients....[and] this study demonstrates the association of a Tcrb V region gene polymorphism with one subtype of JRA in the context of a particular HLA class II allele, HLA-DQA1*0101. These findings thus support a possible contribution by this Tcrb-V gene to at lease one human autoimmune disease, EOP-JRA" (pages 258-260). In summary, Maksymowych teaches a method for genotyping a T cell receptor wherein the methods comprise providing an array (i.e., a dot blot) having immobilized thereon target nucleic acids from a biological sample and contacting the array with labeled probes. Maksymowych does not teach methods for detecting a T cell receptor genotype wherein the

methods comprise providing an array having probes immobilized thereon and contacting the array with target nucleic acids from a biological sample.

However, Shimkets et al. teach that single nucleotide polymorphisms (SNPs) can be detected and genotyped by microarrays, and said genotype can be used to identify SNPs associated with a disease. Shimkets shows that hybridization of sample genomic sequences to allele specific probes on a microarray, and detection of said hybridization can be used to identify SNPs that characteristic of diseases. These "allele-specific probes can be designed that hybridize to a segment of target DNA from one individual but do not hybridize to the corresponding segment from another individual due to the presence of different polymorphic forms in the respective segments of the two individuals.... Allele-specific probes are often used in pairs, one member of a pair showing a perfect match to a reference form of a target sequence and the other member showing a perfect match to a variant form. Several pairs of probes can then be immobilized on the same support for simultaneous analysis of multiple polymorphisms within the same target sequence" (page 34, lines 6-19). Furthermore, Shimkets teach that the results of the array analysis can detect "the presence or absence of a set of polymorphisms (i.e. a polymorphic set) is determined for a set of the individuals, some of whom exhibit a particular trait, and some of which lack of the trait" (page 40, lines 21-23). Moreover, a "strong correlation between a set of one or more polymorphic forms and a disease...such as autoimmune diseases" can be determined (page 40, lines 31-

40 and line 10), and said genotype can be used to for "regular monitoring of the patient (page 41, lines 2-3).

It would have been obvious to one of ordinary skill in the art at the time of the invention was made to have modified the method of Maksymowych so as to have included the use of an array comprising allele-specific probes because Maksymowych teaches that SNPs at TCR variable regions occur at a higher frequency in patients with autoimmune diseases and Shimkets teaches that probe arrays can be used to genotype polymorphisms characteristic of autoimmune diseases which subsequently can monitor a patient. One would have been motivated to have used the probe arrays of Shimkets in order to have achieved the benefit of detecting TCR variable region SNPs that are associated with autoimmune diseases and predicting an immune response of individuals suspected of said disease. One would have been motivated to have used the probe arrays of Shimkets in the genotyping method of Maksymowych in order to have provided a rapid, cost-efficient and effective method for simultaneously analyzing multiple samples and multiple polymorphisms in the TCR gene.

With respect to claims 3 and 4, Maksymowych (page 260, 2nd paragraph), teaches that the disclosed genotyping method is used to correlate the presence of a polymorphism with susceptibility to autoimmune disease wherein the method comprises comparing the TCR hybridization patterns of a population of control individuals with a population of individuals having juvenile rheumatoid arthritis. With respect to claims 5 and 6, Maksymowych also teaches an association between the Tcrb-V genotype and progression of arthritis in JRA. The reference

(page 261) states that the genotyping method is advantageous in that it allows for the segregation of patient's on an immunogenetic basis in order to identify patients at increased risk of suffering progressive disease. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have applied the genotyping method of Maksymowych to a method which determines the outcome (progression) of arthritis in JRA patients in order to have facilitated early intervention and treatment in patients that are found to be more susceptible to progressive disease.

5. Claims 1-6 rejected under 35 U.S.C. 103(a) as being as being unpatentable over Shimkets et al. (WO 01/48245A2) in view of Subrahmanyan (2001, reference C as cited in the IDS).

Shimkets et al. teach that single nucleotide polymorphisms (SNPs) can be detected and genotyped by microarrays, and said genotype can be used to identify SNPs associated with a disease. Shimkets shows that hybridization of sample genomic sequences to allele specific probes on a microarray, and detection of said hybridization can be used to identify SNPs that characteristic of diseases. These "allele-specific probes can be designed that hybridize to a segment of target DNA from one individual but do not hybridize to the corresponding segment from another individual due to the presence of different polymorphic forms in the respective segments of the two individuals.... Allele-specific probes are often used in pairs, one member of a pair showing a perfect match to a reference form of a target sequence and the other member showing a perfect match to a variant form. Several pairs of probes can then be immobilized

on the same support for simultaneous analysis of multiple polymorphisms within the same target sequence" (page 34, lines 6-19). Furthermore, Shimkets teach that the results of the array analysis can detect "the presence or absence of a set of polymorphisms (i.e. a polymorphic set) is determined for a set of the individuals, some of whom exhibit a particular trait, and some of which lack of the trait" (page 40, lines 21-23). Moreover, a "strong correlation between a set of one or more polymorphic forms and a disease...such as autoimmune diseases" can be determined (page 40, lines 31-40 and line 10), and said genotype can be used to for "regular monitoring of the patient (page 41, lines 2-3). Shimkets teaches applying the genotyping method to a variety of genes associated with autoimmune diseases, but does not specifically teach applying the method of genotyping to the TCR gene.

However, Subrahmanyn teaches that several hundred SNPs of the T cell variable have been detected. Subrahmanyan sequenced and identified "279 SNPs in 55,848 bp" within the β unit of the T cell receptor (TCRB), and "the data...provides an excellent starting point for the identification of disease associated with TCRB (page 384 and 392 respectively). Moreover, Subrahmanyn teaches that "these results provide the basis for optimization of locuswide SNP typing in TCRB for studies of genotype-phenotype association" (page 381).

It would have been obvious to one of ordinary skill in the art at the time of the invention was made to have modified the microarray of Shimkets so as to have included the TCRB SNPs as probes on a microarray because Shimkets

teaches that microarrays can be used as a diagnostic tool to genotype characteristic SNPs of autoimmune diseases and correlate said genotype of a patient and control to predict a clinical outcome, and Subrahmanyn teaches that the TCRB has hundreds of SNPs. One would have been motivated to have used the TCRB SNPs identified by Subrahmanyn as probes in order to have achieved the benefit of providing a method which allowed for the detection of a wide variety of TCR variable region SNPs and which could thereby be used to determine the association of said SNPs with autoimmune diseases and for predicting an immune response and clinical outcome in individuals suspected of said disease.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Wong whose telephone number is (571) 272-1120. The examiner can normally be reached on Monday-Friday; 8 AM-4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones can be reached on (571) 272-0745. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jennifer Wong

CARLA J. MYERS
PRIMARY EXAMINER